testing on single cells—for example Duchenne muscular dystrophy.[1] Secondly, it can be used to identify single gene defects such as cystic fibrosis, where the molecular abnormality is testable with molecular techniques after polymerase chain reaction (PCR) amplification of DNA extracted from single cells.[2] Thirdly, it can be used in chromosomal disorders, where fluorescence in situ hybridisation has been developed to detect a variety of chromosomal rearrangements, including translocations, inversions, and chromosome deletions.[3] Some potential parents who carry a chromosomal rearrangement may never have achieved a viable pregnancy before requesting preimplantation genetic diagnosis if each previous conception resulted in a chromosomally unbalanced embryo which miscarried spontaneously.

Preimplantation genetic screening for aneuploidy (Down's syndrome and other trisomies) is not licensed by the Human Fertilisation and Embryology Authority in the United Kingdom, though it is offered elsewhere, including the United States and Italy.

It has taken over 10 years for preimplantation genetic diagnosis to become established, and only five UK centres are licensed. A preimplantation diagnosis cycle is a major undertaking for any couple, and the psychological, medical, and financial costs are considerable. A single cycle costs £4000-7000 (US$6000-10 500) (including drugs). About half of British patients obtain some NHS funding.

Recently the European Society of Human Reproduction and Embryology published results on 886 couples undergoing 1318 cycles of preimplantation genetic diagnosis over seven years.[4] Most couples had already had pregnancies, but fewer than 25% had healthy children. Over a quarter had one or more children affected with a genetic condition and a similar proportion had a spontaneous abortion or underwent termination after prenatal diagnosis. In about a third of cases the genetic indication for preimplantation genetic diagnosis was combined with subfertility, necessitating in vitro fertilisation or intracytoplasmic sperm injection. The reported pregnancy rate was only 17% (detection of fetal heart beat per cycle started), but this is improving: in our centre, established in 1998, the rate is 33%.[5] The European study reported four misdiagnoses after tests using PCR; these were detected at prenatal diagnosis, which was performed on 116 of the 236 fetal sacs (49%).[4]

The high incidence of multiple pregnancies after preimplantation genetic diagnosis is a concern (33% from the European data). Probably a maximum of two embryos should be transferred. Data so far suggest that children born after preimplantation genetic diagnosis do not have a higher incidence of congenital malformations or neonatal problems than children born after "regular" intracytoplasmic sperm injection, but they need to be followed up systematically through childhood.[4]

In the United Kingdom the Human Fertilisation and Embryology Authority has a central role in regulating preimplantation diagnosis, and each centre must obtain a licence for every test offered. The submission of multiple applications is time consuming and there is a debate in the UK about whether over-regulation is stifling service development. The authority's strong guidance is important, however, in such a new and controversial area. The virtually unregulated provision of preimplantation diagnosis in other countries, where sex selection for "family balancing" and HLA typing is performed, risks bringing the whole technique into disrepute.

To offer a safe effective service, a multidisciplinary team needs to be established, including specialists in in vitro fertilisation, clinical geneticists, genetic counsellors, cytogeneticists, and molecular biologists. Laboratories should participate in external quality assessment. The UK's tight regulation should reassure people worried that preimplantation diagnosis might lead to "designer babies." Establishing a similar degree of regulation internationally will depend on the motivation of individual governments and clinicians.

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The promise of human genetic databases

High ethical as well as scientific standards are needed

Genetic databases are now helping elucidate gene function, estimate the prevalence of genes in populations, differentiate among subtypes of diseases, trace how genes may predispose to or protect against illnesses, and improve medical intervention. They achieve this by bringing together several streams of data about individuals: molecular genetic data; high quality standardised clinical data; data on health, lifestyle, and environment; and in some cases, genealogical data.

The main strategy with genetic databases is to search, often by statistical brute force, for correlations, then use the genetic focusing to guide mechanistic, pharmaceutical, and other investigations. Searching for

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causal associations between genetic and health phenomena is not new. While marvelling at our glossy new human genome posters we mustn't forget the huge contributions to research, care, and counselling—and genome mapping—that continue to be made by many data collections on the classic mendelian disorders. What is revolutionary is the precision with which genetic makeup can now be known, at reasonable cost and speed, and the discrimination with which genetic details can be correlated, via computer, with other complex information.[1 2]

Thus pharmacogeneticists are probing databases for gene related variabilities in drug responsiveness and metabolism. The vision is to tailor drugs to particular constitutions and to screen for genetic suitability before prescribing.[3–5] Asthma, migraine, Alzheimer's disease, depression, psoriasis, and osteoarthritis are among the diseases being attacked. Most pharmaceutical and biotechnology companies are building or buying access to genetic databases and DNA libraries, often formed around data from clinical trials.

Studies of genetically influenced variability also are aiding toxicological investigations, the sorting out of causes of adverse drug events, and the delineating of genetic pathology in some cancers. They are beginning to reveal how genes express themselves in early development, menarche, menopause, ageing, and perceptual and behavioural illnesses.

Some database initiatives are governmental, some private, and some hybrid. One of the most well known and controversial is the Icelandic health sector database, managed by the firm deCODE Genetics, into which general practitioners routinely deposit patient data. Research, a prime purpose, is aided by the fact that Icelanders' genealogies are well known. Citizens may opt out, and the anonymisation of data and the protection of subjects are overseen by several supervisory bodies. Currently Icelanders are debating whether they should agree to nationwide submission of blood samples for DNA mapping.[6] Similar national or regional initiatives, organised in differing ways but usually financed in part by sale of data access and intellectual property rights, are being explored in Estonia, Newfoundland, China, Singapore, and Tonga.

Many other, less dramatic, projects are already well underway. The Danish National Birth Cohort Study of 100 000 pregnancies is mapping the DNA of mothers and their babies to probe the causes of congenital disorders and other problems.[7] The Acute Coronary Event DNA Library project is correlating subjects' gene sequences with epidemiological data to try to understand genetic factors in premature coronary artery disease.[8] The Avon Longitudinal Study of Parents and Children is studying the interplay between genes and environment in childhood infection, allergies, asthma, and development in 14 000 children born in 1991-2, so far amassing over 127 million data points from questionnaires, studies of home environments, clinical examinations, and DNA analyses.[8]

Now an ambitious Population Biomedical Collection (on www.wellcome.ac.uk/en/1/biovenpop.html) is being planned in the United Kingdom, to study common multifactorial midlife illnesses such as diabetes, Alzheimer's disease, and early onset heart disease.[6] Supported mainly by the Wellcome Trust, the Medical Research Council, and the Department of Health, the project will probably be managed through a non-profit organisation. The database, covering some 500 000 volunteers aged 45-64, will interlink NHS clinical files; health, lifestyle, and environmental histories recorded by NHS research nurses; and gene maps of DNA extracted from blood samples. Full prior consent, including agreement to periodic follow up, will, of course, be sought.

Ethical requirements for genetic databases

- Follow respectful protocols in approaching people and eliciting medical histories and information about relatives
- Secure informed consent to broad, perhaps open ended, study, and also maybe commercial application of findings
- Manage anonymisation interlinking of databases, and other privacy issues
- Establish confidentiality and security safeguards
- Develop defensible responses to requests for personal data by public health authorities, police, courts, employers, lenders, insurers, and subjects' relatives
- Devise sound data access, ownership, and intellectual property policies
- Be clear about whether and how individuals will be informed of findings that might be medically helpful to them
- Arrange supervision by research ethics and privacy protection bodies

Prompted in part by this proposal, the House of Lords Select Committee on Science and Technology has conducted an inquiry on human genetic databases.[8] This inquiry complements the Human Genetics Commission's development of "strategic advice on the 'big picture' of human genetics, with a particular focus on social and ethical issues." The commission has just finished consulting on the future use of genetic information and the protection people want. This revealed broad support for the benefits offered by human genetic research, but some misgivings about the regulation of such developments (www.hgc.gov.uk).

The ethical and policy challenges attending genetic databases are no less complex than the challenges of scientific design (see box).[6 9] Since no major genetic database is likely to deliver its potential unless the public recognises it as a common good, proponents must seek public agreement on these ethics and policy issues and make the case for pursuing the research for collective benefit.

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